(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 September 2002 (12.09.2002)

PCT

(10) International Publication Number
WO 02/070464 A2

(51) International Patent Classification[7]: C07C 251/86, A61K 31/15, A61P 31/04, C07D 207/325

(21) International Application Number: PCT/EP02/00474

(22) International Filing Date: 18 January 2002 (18.01.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCT/EP01/00636 22 January 2001 (22.01.2001) EP

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/070464 A2

(54) Title: NOVEL HYDRAZONES

(57) Abstract: The invention relates to novel hydrazone derivatives and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more of those compounds and especially their use as anti-infectives.

Novel Hydrazones

The present invention relates to novel hydrazones of the general formula **1** , to a process for the manufacture of these hydrazones, to pharmaceutical compositions containing them and to their use in the treatment of microbial infections.

Related hydrazones have been investigated previously, especially with regard to their potential as antitumor agents: see Antonini et al., *J. Med. Chem.* **1981**, *24*, 1181-1184. Notably PIH (Pyridoxal Isonicotinoyl Hydrazone) seem to display pronounced antiproliferative activity: Richardson, D.R.; Milnes, K. *Blood* **1997**, *89*, 3025-38. Moreover, azinyl and diazinyl hydrazones appear to act similarly: Easmon, J.; Heinisch, G.; Pürstinger, G.; Langer, T.; Osterreicher, J.K.; Grunicke, H.H.; Hofmann, J. *J. Med. Chem.*, **1997**, *40*, 4420-4425. The inhibition of tumor growth seems to be linked to the iron (III) chelating property of PIH: Richardson, D.R. *Antimicrob. Agents Chemother.* **1997**, *41*, 2061-2063.

So far only peptides have been uncovered to inhibit the bacterial phosphotransferase system (PTS) which is a drug target system useful for identifying new anti-microbials. It has now been found that most of the hydrazones of formula **1** of the present invention are potent inhibitors of enzyme I of the bacterial phosphotransferase system ("PTS") (compare table 1). Inhibition of enzyme I is expected to decrease bacterial virulence and pathogenicity, as demonstrated by gene knock-out studies (Eur. Pat. Appl. EP 0 866 075). Consequently, low molecular weight organic compounds affecting this phosphorylation cascade may be useful in the treatment of bacterial infections in human and/ or veterinary medicine.

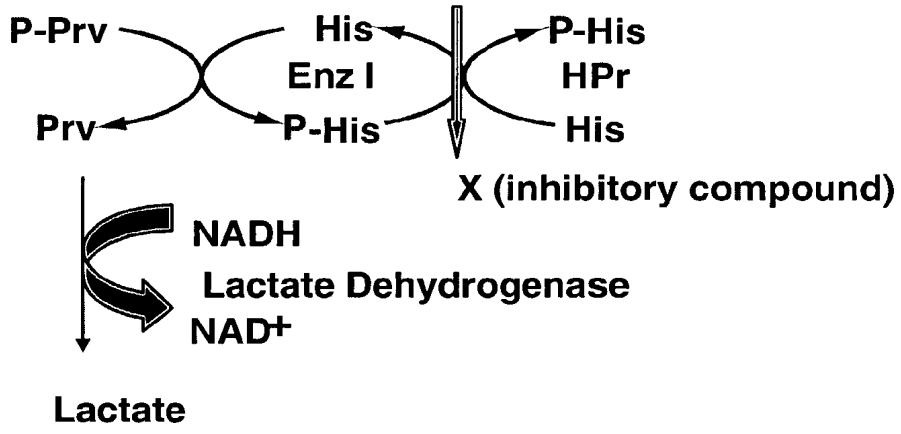
It has also been found that a number of these compounds, that are active in PTS, exhibit antibacterial activity. Several compounds of formula **1** are very specific in exhibiting antibacterial activity consequently these compounds of formula **1** are generally useful to combat bacterial pathogens in human and

animals, e.g. to combat Gram positive pathogens such as Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus faecalis or Streptococcus pneumoniae etc., and Gram negatives like Haemophilus influenzae, Escherichia coli, Klebsiella pneumoniae or Proteus vulgaris.

The determination of activity of a compound of the present invention in the PTS may be summarized as follows:

Assay for enzyme I dependent PEP: peptide phosphotransferase activity.

PTS- Inhibition Assay



To find inhibitors of Enzyme I of the PTS by high throughput screening, an *in vitro* assay based on spectrophotometric read out at 340nm has been set up. The assay comprises of three major components, purified enzyme I in catalytic amounts, Phosphoenol Pyruvate (PEP) as the phosphoryl donor substrate and purified HPr as the phosphoryl acceptor substrate.

The assay couples the formation of pyruvate formed from PEP to lactate, catalyzed by lactate dehydrogenase. The disappearance of NADH, cofactor required by lactate dehydrogenase, is determined spectrophotometerically at 340

nm. The assay is done in a U-shaped microtiter plate format, and quantitation is done using microplate absorbance reader.

100 µl reaction mixture contained 0.8 mM PEP, 0.2 mM NADH, 3 µg lactate dehydrogenase (Boehringer Mannheim), 50 mM KP_i pH=7.5, 2.5 mM dithiothreitol, 2.5 mM NaF, 5 mM $MgCl_2$, and between 50 and 100 µM of the compound. The reaction is started by the addition of enzyme I (final concentration 0.75 µM). In a control experiment the compound is replaced by DMSO.

The results obtained are summarized table 1.

Table1

Compounds	Example	Synthetic method	Inhibition of PTS (IC50 in uM)
N'-(2,5-Dihydroxy-benzylidene)-benzohydrazide	1	A	15
N'-(2-Hydroxy-benzylidene)-2-(1H-indol-3-yl)-acetohydrazide	2	A	50
N'-(2,5-Dihydroxy-benzylidene)-naphthalene-1-carbohydrazide	3	A	6
3,4,5-Trimethoxy-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	4	A	15
2-Amino-5-chloro-N'-(2-hydroxy-benzylidene)-benzohydrazide	5	A	6
3-Trifluoromethyl-N'-(2,4-dihydroxy-benzylidene)-benzohydrazide	6	A	10
3-Methoxy-N'-[1-(2-hydroxy-phenyl)-ethylidene]-benzohydrazide	7	B	8
3-Methoxy-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide	8	A	15
3,4-Dichloro-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	9	A	75

4-Chloro-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide	10	A	8
4-Hydroxy-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide	11	A	0.5
3,4-Dichloro-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide	12	A	0.7
3-Chloro-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide	13	A	0.7
4-Hydroxy-3-methoxy-N'-(5-chloro-2-hydroxy-benzylidene)-benzohydrazide	14	A	25
N'-[1-(2,5-Dihydroxy-phenyl)-ethylidene]-benzohydrazide	15	A	6
N'-(2,5-Dihydroxy-benzylidene)-4-hydroxy-3-methoxy-benzohydrazide	16	A	4
N'-(2-Hydroxy-5-methyl-benzylidene)-benzohydrazide	17	A	6
2-Methylamino-N'-(5-chloro-2-hydroxy-benzylidene)-benzohydrazide	18	A	4
2-Methylamino-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide	19	A	2
3-Methyl-N'-(5-chloro-2-hydroxy-benzylidene)-benzohydrazide	20	A	4
3-Trifluoromethyl-N'-(5-chloro-2-hydroxy-benzylidene)-benzohydrazide	21	A	12
2-Methylamino-N'-[1-(2-hydroxy-phenyl)-7ethylidene]-benzohydrazide	22	A	2
N-[2-[1-(2-Benzoyl-hydrazono)-ethyl]-phenyl]-acetamide	23	A	250
4-Chloro-N'-[1-(2-amino-phenyl)-ethylidene]-benzohydrazide	24	B	0.8
3-Methoxy-N'-[1-(2-Amino-phenyl)-ethylidene]-benzohydrazide	25	B	20

N'-(2,3-Dihydroxy-benzylidene)-benzohydrazide	26	A	50
3-Methoxy-N'-(2-hydroxy-benzylidene)-benzohydrazide	27	A	7
N'-(2,3,4-Trihydroxy-benzylidene)-benzohydrazide	28	A	3
N'-(2,4,5-Trihydroxy-benzylidene)-benzohydrazide	29	A	25
3,4,5-Trimethoxy-N'-(2,4,5-trihydroxy-benzylidene)-benzohydrazide	30	A	25
4-Bromo-N'-(2-hydroxy-benzylidene)-benzohydrazide	31	A	75
3-Trifluoromethyl-N'-(2-hydroxy-benzylidene)-benzohydrazide	32	A	7
3-Methyl-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide	33	A	2
3-Trifluoromethyl-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide	34	A	15
4-Hydroxy-N'-[1-(2,5-dihydroxy-phenyl)-ethylidene]-benzohydrazide	35	B	1.75
4-chloro-N'-(2-hydroxy-3-chloro-benzylidene)-benzohydrazide	36	A	100
4-Chloro-N'-(2,4-dihydroxy-benzylidene)-benzohydrazide	37	A	20
3-Chloro-N'-(2-hydroxy-5-chloro-benzylidene)-benzohydrazide	38	A	75

Biological results

Antimicrobial susceptibility testing was performed in accordance with the National Committee for Clinical Laboratory Standards (NCCLS) procedure [M7-A5, 2001: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard -Fifth Edition American National Standard].

The results are obtained are summarized in table 2.

Table2 *In vitro* Antibacterial Activity of Compounds

(Minimum Inhibitory Concentration (MIC) in micrograms/ml)

Name	exa mple	Synthetic method	Escherichia coli DC2	Staphylococcus aureus ATCC25923	Staphylococcus aureus 101
N'-(2,5-Dihydroxy-benzylidene)-benzohydrazide	1	A	128	64	nt
3,4,5-Trimethoxy-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	4	A	128	128	nt
3-Trifluoromethyl-N'-(2,4-dihydroxy-benzylidene)-benzohydrazide	6	A	32	na	nt

3,4-Dichloro-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	9	A	32	8	nt
4-Chloro-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide	10	A	na	128	nt
4-Hydroxy-3-methoxy-N'-(5-chloro-2-hydroxy-benzylidene)-benzohydrazide	14	A	128	128	nt
3-Trifluoromethyl-N'-(5-chloro-2-hydroxy-benzylidene)-benzohydrazide	21	A	na	16	nt
4-Methoxy-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	39	A	64	64	64
3,4-Dichloro-N'-(2,3-dihydroxy-benzylidene)-benzohydrazide	40	A	na	4	4
3,5-Bis-(trifluoromethyl)-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	41	A	na	64	64
3-Chloro-2-pyrrol-1-yl-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	42	A	128	32	32

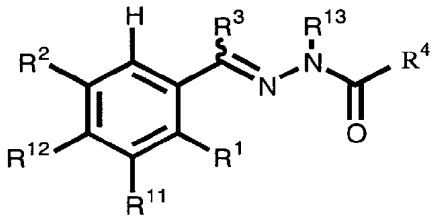
3-Chloro-2-pyrrol-1-yl-N'-(2-hydroxy-3,5-dichloro-benzylidene)-benzohydrazide	43	A	na	2	2
2-Pyrrol-1-yl-N'-(2,4,5-trihydroxy-benzylidene)-benzohydrazide	44	A	128	64	64
4-Chloro-3-trifluoromethyl-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	45	A	2	0.5	1
4-Chloro-3-trifluoromethyl-N'-(2-hydroxy-3,5-dichloro-benzylidene)-benzohydrazide	46	A	na	128	128
4-Chloro-N'-(2,4,5-trihydroxy-benzylidene)-benzohydrazide	47	A	64	8	nt
N'-(2-Hydroxy-3,5-dichloro-benzylidene)-benzohydrazide	48	A	na	128	nt
3-Chloro-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	49	A	64	16	nt
3-Trifluoromethyl-N'-(2,4,5-trihydroxy-benzylidene)-benzohydrazide	50	A	na	32	nt

3-Trifluoromethyl-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	51	A	64	8	nt
3,4-Dichloro-N'-[1-(2,3,4-dihydroxy-phenyl)-ethylidene]-benzohydrazide	52	A	64	4	nt
3,4-Dichloro-N-methyl-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	53	A	na	128	nt

na means not active at concentrations less than 128 μg/ml

nt means not tested

The present invention relates to novel hydrazones of the general formula **1**,



1

wherein R^1 represents lower alkyl-carbonylamino; formylamino; amino; hydroxy;

R^2 represents hydrogen; hydroxy; lower alkyl; fluoro; chloro;

R^3 represents hydrogen; methyl; ethyl; isopropyl;

R^{11} represents hydrogen; hydroxy; lower alkyl; lower alkoxy; fluoro; chloro; amino;

R^{12} represents hydrogen; hydroxy; lower alkyl; lower alkoxy; fluoro; chloro; amino

R^{13} represents hydrogen; lower alkyl

R^4 represents aryl; arylmethyl; indoyl methyl; mono-, di- or tri- substituted aryl, arylmethyl, which substituents may be lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy, N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl and which substituents may be the same or different;

in case R^1 represents amino and R^2, R^{11}, R^{12}, R^{13} and R^3 represent hydrogen, R^4 is not unsubstituted phenyl; phenylmethyl; 2-amino-phenyl; 2-hydroxy-phenyl; 4-chloro-phenyl;

in case R^1 represents amino and R^2, R^{11}, R^{12} and R^{13} represent hydrogen and R^3 represents methyl, R^4 is not unsubstituted phenyl; 2-hydroxy-phenyl;

in case R^1 represents methyl-carbonylamino and R^2, R^3, R^{11}, R^{13} and R^{12} represent hydrogen, R^4 is not 4-hydroxy-3-methoxy-phenyl;

in case R^1 is hydroxy and R^2, R^{11}, R^{12} and R^{13} represent hydrogen and R^3 represents methyl, R^4 is not unsubstituted phenyl; 4-methyl-phenyl; 2-methyl-phenyl; 2-hydroxy-phenyl; 4-methoxy-phenyl; 4-chloro-phenyl; 2-chloro-phenyl; 2,4,6-trimethyl-phenyl;

in case R^1 is hydroxy and R^2, R^{11}, R^{12} and R^{13} represent hydrogen and R^3 represents ethyl, R^4 is not unsubstitued phenyl or 2-hydroxy-phenyl;

in case R^1 is hydroxy and R^2, R^{11}, R^{12} and R^3 represent hydrogen and R^{13} represents methyl, R^4 is not unsubstituted phenyl;

in case R^1 is hydroxy and R^2, R^{11}, R^{12}, R^{13} and R^3 represent hydrogen, R^4 is phenyl substituted with 2-trifluoromethyl, 3-trifluoromethyl, 3-methoxy or (2-amino-5-chloro);

in case R^1 and R^{11} represent hydroxy and R^2, R^3, R^{12} and R^{13} represent hydrogen, R^4 is not 2-chloro-phenyl;

in case R^1 is hydroxy and R^{11} is methoxy and R^2, R^3, R^{12} and R^{13} represent hydrogen, R^4 is not unsubstituted phenyl; 2-hydroxy-phenyl; 2-chloro-phenyl; 4-hydroxy-3-methoxy-phenyl; 5-chloro-2-hydroxy-phenyl; 2-(3-hydroxy)-naphthyl; 2,4-dichloro-phenyl; 4-amino-3,5-dichloro-phenyl; 5-bromo-2-hydroxy-phenyl;

in case R^1, R^{11} and R^{12} represent hydroxy and R^2 and R^{13} represent hydrogen and R^3 is methyl, R^4 is not unsubstituted phenyl;

in case R^1 and R^{12} represent hydroxy and R^2, R^3, R^{11} and R^{13} represent hydrogen, R^4 is not unsubstituted phenyl; 2-hydroxy-phenyl; 4-methoxy-phenyl; 4-hydroxy-3-methoxy-phenyl; 2,4-dichloro-phenyl;

in case R^1 and R^{12} represent hydroxy and R^2, R^{11} and R^{13} represent hydrogen and R^3 is methyl, R^4 is not unsubstituted phenyl; 2-hydroxy-phenyl;

in case R^1 is hydroxy and R^{12} is methoxy and R^2, R^3, R^{11} and R^{13} represent hydrogen, R^4 is not 4-hydroxy-3-methoxy-phenyl;

in case R^1 is hydroxy and R^{12} is methoxy and R^2, R^{11} and R^{13} represent hydrogen and R^3 is methyl, R^4 is not unsubstituted phenyl;

in case R^1 is hydroxy and R^2 is chloro and R^3, R^{11}, R^{12} and R^{13} represent hydrogen, R^4 is not unsubstituted phenyl; 2-methyl-phenyl; 2-hydroxy-phenyl; 4-hydroxy-phenyl; 4-methoxy-phenyl; 4-chloro-phenyl; 5-chloro-2-hydroxy-phenyl; 2-hydroxy naphth-1-yl; 3-hydroxy naphth-2-yl; 2,4-dichloro-phenyl; 3,4-dichloro-phenyl; 3,4,5-trihydroxy-phenyl; 5-bromo-2-hydroxy-phenyl;

in case R^1 is hydroxy and R^2 and R^{11} represent chloro and R^3, R^{12} and R^{13} represent hydrogen, R^4 is not 2-hydroxy-phenyl; 5-chloro-2-hydroxy-phenyl; 3-hydroxy naphth-2-yl; 2-hydroxy-3,5-dichloro-phenyl; 5-bromo-2-hydroxy-phenyl; 3,5-dibromo-2-hydroxy-phenyl; N-pyrrolyl;

in case R^1 is hydroxy and R^2 and R^3 represent methyl and R^{11}, R^{12} and R^{13} represent hydrogen, R^4 is not unsubstituted phenyl;

in case R^1 is hydroxy and R^2 is methyl and R^3, R^{11}, R^{12} and R^{13} represent hydrogen, R^4 is not 4-chloro-phenyl; 2-naphthyl; 2-bromo-phenyl; 3-bromo-phenyl; 4-bromo-phenyl;

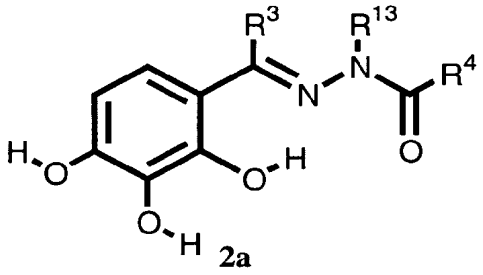
in case R^1 is hydroxy and R^2 is fluoro and R^{11}, R^{12} and R^{13} represent hydrogen and R^3 is methyl or ethyl, R^4 is not 4-fluoro methyl;

in case R^1 and R^{12} represent hydroxy and R^{11} is chloro and R^3 and R^{13} represent hydrogen and R^2 is n-butyl or (3-methyl)-butyl or n-pentyl, R^4 is not 4-amino-2-hydroxy-phenyl;

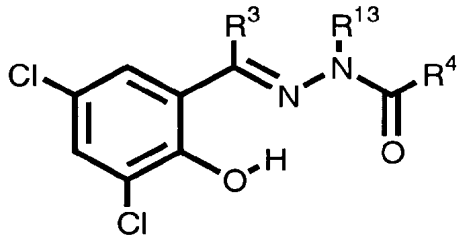
in case R^1 and R^{12} represent hydroxy and R^2 is ethyl or n-butyl or n-hexyl or (3-methyl)-butyl and R^3, R^{11} and R^{13} represent hydrogen, R^4 is not unsubstituted phenyl, 4-amino-phenyl, 4-hydroxy-phenyl, 2-hydroxy-phenyl, 4-amino-2-hydroxy-phenyl,

and pharmaceutically acceptable salts thereof.

Preferred compounds are compounds of the formulae **2a-2e**,



2a



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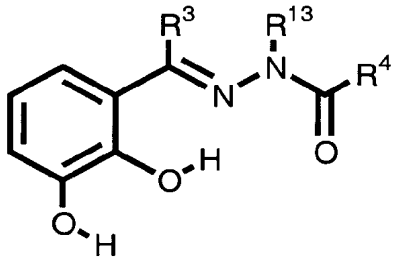

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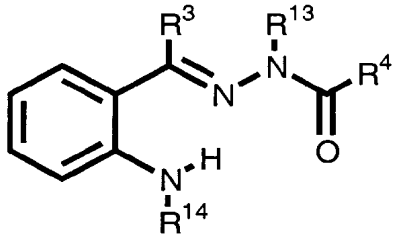
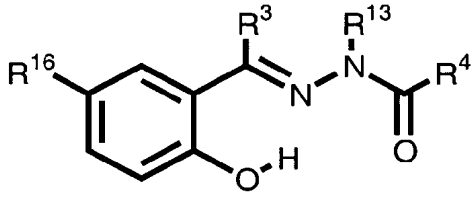


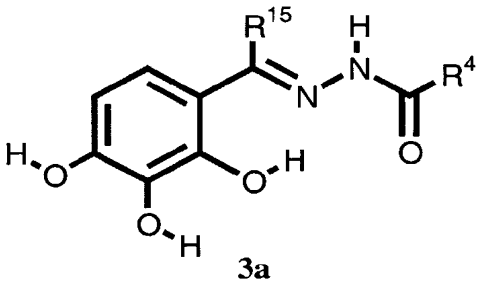
2d



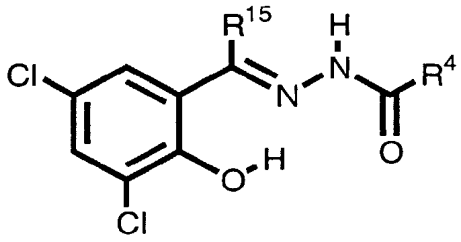
2e

wherein R^3, R^{13} and R^4 have the meaning given in formula **1** and R^{14} is hydrogen, lower alkyl , formyl or acetyl and R^{16} is hydrogen, methyl, fluoro, chloro, hydroxy or ethyl and pharmaceutically acceptable salts thereof.

Very preferred compounds are compounds of the formulae **3a-3e**,



3a



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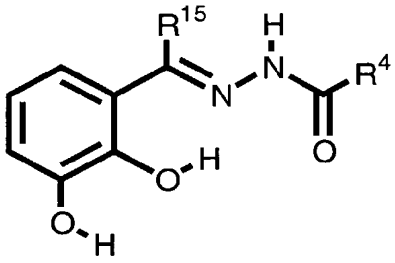

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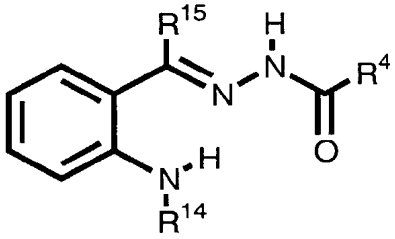
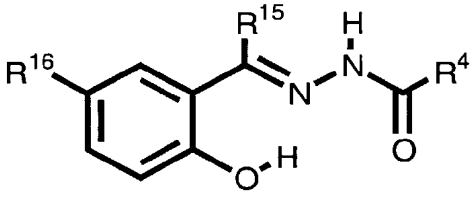


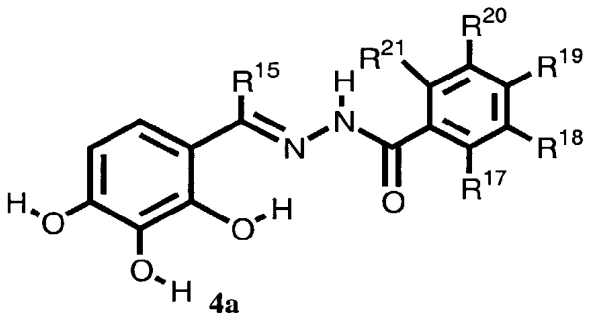
3d



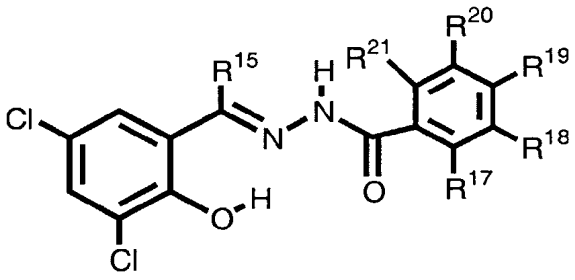
3e

wherein $\mathbf{R^4}$ has the meaning given in formula **1** and $\mathbf{R^{14}}$ is hydrogen, lower alkyl , formyl or acetyl and $\mathbf{R^{16}}$ is hydrogen, methyl, fluoro, chloro, hydroxy or ethyl and $\mathbf{R^{15}}$ is hydrogen, methyl or ethyl and pharmaceutically acceptable salts thereof.

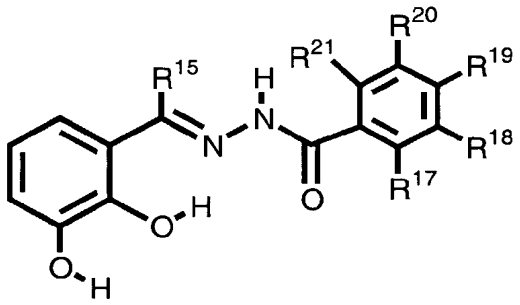
Especially preferred compounds are compounds of the formulae **4a-4f**.



4a



4b



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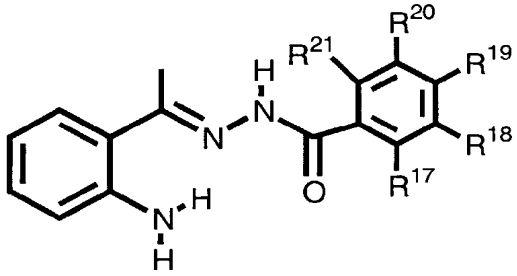

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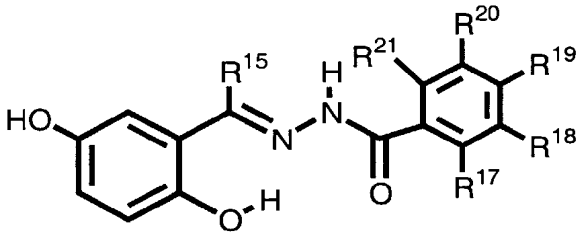
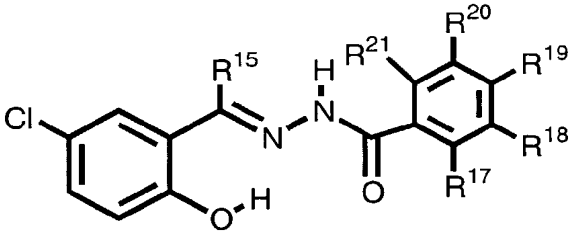


4e



4f

In formula **4a** R^{15} represents hydrogen, methyl or ethyl and, R^{17}, R^{18}, R^{19}, R^{20} and, R^{21}, which may be the same or different, represent hydrogen, N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy, in case R^{15} is methyl either one or two of the substituents R^{17}, R^{18}, R^{19}, R^{20}, R^{21} represent N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy.

In formula **4b** R^{15} represents hydrogen, methyl or ethyl and R^{17}, R^{18}, R^{19}, R^{20} and R^{21}, which may be the same or different, represent hydrogen, N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy, in case R^{17} is N-pyrrolyl either one or two of the substituents R^{18}, R^{19}, R^{20}, R^{21} represent lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy.

In formula **4c** R^{15} represents hydrogen, methyl or ethyl and R^{17}, R^{18}, R^{19}, R^{20} and R^{21}, which may be the same or different, represent hydrogen, N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy, in case R^{15} is hydrogen and R^{17} is chloro either one or two of the substituents R^{18}, R^{19}, R^{20}, R^{21} represents, N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino or lower alkylendioxy.

In formula **4d** R^{17}, R^{18}, R^{19}, R^{20} and R^{21}, which may be the same or different, represent hydrogen, N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy, in case R^{17} is hydrogen or hydroxy, either one or two of the substituents R^{18}, R^{19}, R^{20}, R^{21} represent N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy.

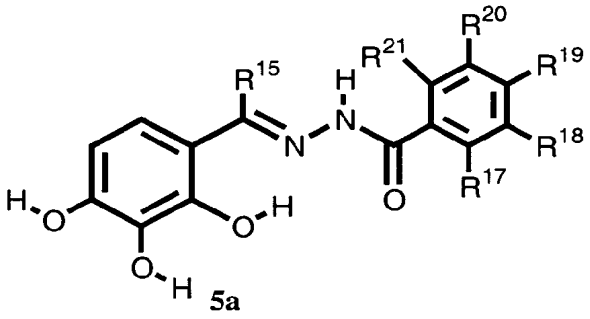
In formula **4e** R^{15} represents hydrogen, methyl, ethyl and R^{17}, R^{18}, R^{19}, R^{20} and R^{21}, which may be the same or different, represent hydrogen, N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy.

In formula **4f** R^{15} represents hydrogen, methyl, ethyl and R^{17}, R^{18}, R^{19}, R^{20} and R^{21}, which may be the same or different, represent hydrogen, N-pyrrolyl, 2-

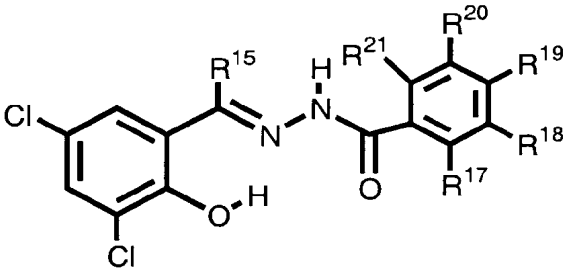
pyrrolyl, 3-pyrrolyl, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy, in case R^{15} is hydrogen then at least one of the substituents R^{17}, R^{18}, R^{19}, R^{20} or R^{21} represents pyrrolyl, trifluoromethyl, or lower alkylamino

and pharmaceutically acceptable salts thereof.

Most preferred compounds are all end products mentioned in examples 1 to 53 including compounds of the formula **5a-e** and pharmaceutically acceptable salts thereof.



5a



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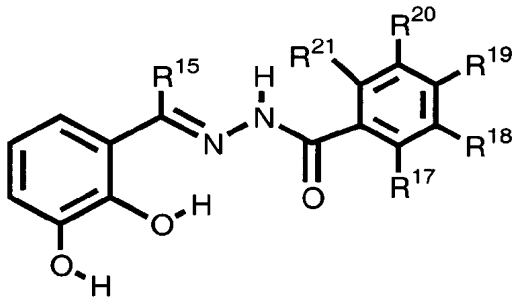
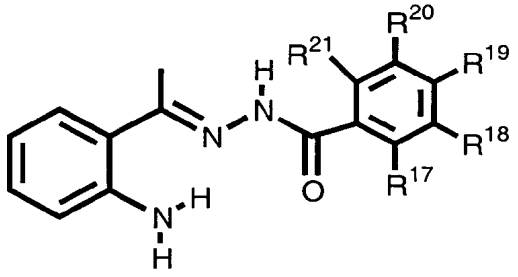
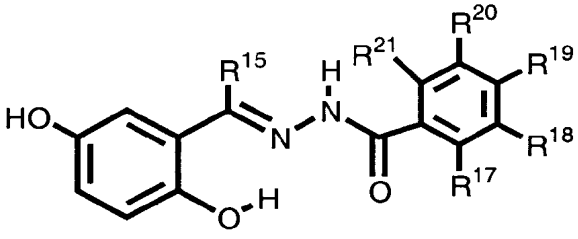


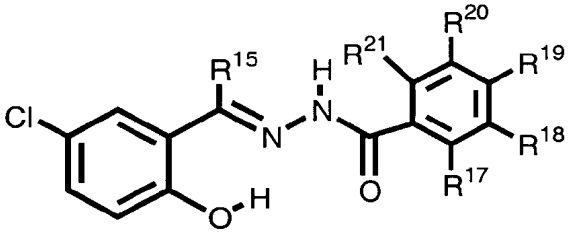
5c



5d



5e



5f

In formula **5a** R^{15} represents hydrogen, methyl or ethyl and R^{17}, R^{18}, R^{19}, R^{20} and R^{21} , which may be the same or different, represent hydrogen, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, lower alkylamino,

lower alkylendioxy, with the proviso that one or two of the substituents R^{17}, R^{18}, R^{19}, R^{20} and R^{21} represent trifluoromethyl or chloro.

In formula **5b** R^{15} represents hydrogen, methyl or ethyl and R^{17}, R^{18}, R^{19}, R^{20} and R^{21} , which may be the same or different, represent hydrogen, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, lower alkylamino, lower alkylendioxy, N-pyrrolyl, 2-pyrrolyl or 3-pyrrolyl, with the proviso that one or two of the substituents R^{17}, R^{18}, R^{19}, R^{20} and R^{21} represent N-pyrrolyl, 2-pyrrolyl or 3-pyrrolyl, in case R^{17} represents N-pyrrolyl, at least one of the substituents R^{18}, R^{19}, R^{20} of R^{21} represents lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, lower alkylamino, lower alkylendioxy.

In formula **5c** R^{15} represents hydrogen, methyl or ethyl and R^{17}, R^{18}, R^{19}, R^{20} and R^{21} , which may be the same or different, represent hydrogen, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, lower alkylamino, lower alkylendioxy, with the proviso that one or two of the substituents R^{17}, R^{18}, R^{19}, R^{20} and R^{21} represent chloro or trifluoromethyl.

In formula **5d** R^{17}, R^{18}, R^{19}, R^{20} and R^{21}, which may be the same or different, represent hydrogen, lower alkyl, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy, with the proviso that one or two of the substituents R^{17}, R^{18}, R^{19}, R^{20} and R^{21} represent chloro, methoxy, methyl or trifluoromethyl.

In formula **5e** R^{15} represents hydrogen, methyl, ethyl and R^{17}, R^{18}, R^{19}, R^{20} and R^{21}, which may be the same or different, represent hydrogen, N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy, with the proviso that one or two of the substituents R^{17}, R^{18}, R^{19}, R^{20} and R^{21} represent chloro, methoxy, methyl of trifluoromethyl.

In formula **5f** R^{15} represents hydrogen, methyl, ethyl and R^{17}, R^{18}, R^{19}, R^{20} and R^{21}, which may be the same or different, represent hydrogen, N-pyrrolyl, 2-

pyrrolyl, 3-pyrrolyl, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy, with the proviso that in case R^{15} is hydrogen at least one of the substituents R^{17}, R^{18}, R^{19}, R^{20} and R^{21} represents N-pyrroly, 2-pyrrolyl, 3-pyrrolyl, trifluoromethyl or lower alkylamino.

In the definitions of the general formula **1** – if not otherwise stated – the expression ***lower*** means straight and branched chain groups with one to seven carbon atoms, preferably 1 to 4 carbon atoms. Examples of lower alkyl and lower alkoxy groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.- butyl, tert.-butyl, pentyl, hexyl, heptyl, methoxy, ethoxy, propoxy, butoxy, iso-butoxy, sec.-butoxy and tert.-butoxy. The expression ***aryl*** represents unsubstituted as well as mono-, di- or tri-substituted aromatic rings with 6 to 10 carbon atoms like phenyl or naphthyl rings which may be substituted with halogen, hydroxy, lower alkyl, lower alkoxy, or lower alkylendioxy forming with the phenyl ring a five- or six-membered ring, trifluoromethyl, lower alkylamino.

The expression pharmaceutically acceptable salts encompasses either salts with inorganic acids or organic acids like hydrohalogenic acids, e.g. hydrochloric or hydrobromic acid; sulfuric acid, phosphoric acid, nitric acid, citric acid, formic acid, acetic acid, maleic acid, tartaric acid, methane sulfonic acid, p-toluene sulfonic acid and the like or in case the compound of formula **1** is acidic in nature with an inorganic base like an alkali or earth alkali base, e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide etc.

Because of their ability to inhibit Gram positive and Gram negative bacteria, the described compounds can be used for the treatment of diseases which are associated with an infection by such type of pathogens. They are valuable anti-infectives.

The compounds can be administered orally, rectally, parenterally, e.g. by intravenous, intramuscular, subcutaneous, intrathecal or transdermal administration or sublingually or as ophthalmic preparation or administered as aerosol. Examples of applications are capsules, tablets, orally administered

suspensions or solutions, suppositories, injections, eye-drops, ointments or aerosols/nebulizers.

Preferred applications are intravenous, intra-muscular, or oral administrations as well as eye drops. The dosage used depends upon the type of the specific active ingredient, the age and the requirements of the patient and the kind of application. Generally, dosages of 0.1 – 50 mg / kg body weight per day are considered. The preparations with compounds of formula **1** can contain inert or as well pharmacodynamically active excipients like sulphonamides. Tablets or granules, for Example, could contain a number of binding agents, filling excipients, carrier substances or diluents.

These compositions may be administered in enteral or oral form e.g. as tablets, dragees, gelatine capsules, emulsions, solutions or suspensions, in nasal form like sprays or rectally in form of suppositories. These compounds may also be administered in intramuscular, parenteral or intraveneous form, e.g. in form of injectable solutions.

These pharmaceutical compositions may contain the compounds of formula **1** as well as their pharmaceutically acceptable salts in combination with inorganic and/or organic excipients which are usual in the pharmaceutical industry like lactose, maize or derivatives thereof, talcum, stearinic acid or salts of these materials.

For gelatine capsules vegetable oils, waxes, fats, liquid or half-liquid polyols etc. may be used. For the preparation of solutions and syrups e.g. water, polyols, saccharose, glucose etc. are used. Injectables are prepared by using e.g. water, polyols, alcohols, glycerin, vegetable oils, lecithin, liposomes etc. Suppositories are prepared by using natural or hydrogenated oils, waxes, fatty acids (fats), liquid or half-liquid polyols etc.

The compositions may contain in addition preservatives, stabilisation improving substances, viscosity improving or regulating substances, solubility improving

substances, sweeteners, dyes, taste improving compounds, salts to change the osmotic pressure, buffer, anti oxidants etc.

The compounds of formula **1** may also be used in co-therapy with one or more other therapeutically used classes of antimicrobial substances, for example, beta-lactams e.g. penicillins and cephalosporins; glycopeptides; quinolones; tetracyclines; aminoglycosides; macrolides etc.

The dosage may vary within wide limits but should be adapted to the specific situation. In general the dosage given in oral form should daily be between about 3 mg and about 4 g, preferably between about 0.2 g and about 4 g, especially preferred between 0.2 g and 2 g per adult with a body weight of about 70 kg. The dosage should be administered preferably in 1 to 3 doses per day which are of equal weight. As usual children should receive lower doses which are adapted to body weight and age.

The invention also relates to a process for the manufacture of compounds of formula **1**, which process comprises reacting

a) equimolar amounts of an aromatic carboxylic acid hydrazide and an aromatic aldehyde at ambient temperature, until the respective hydrazone precipitates, (Method A), or

b) equimolar amounts of an aromatic carboxylic acid hydrazide and an aromatic aldehyde at reflux temperature of the solvent, until the respective hydrazone precipitates (Method B).

A preferred solvent in step B is ethanol.

Examples

The following examples illustrate the invention but do not limit the scope thereof. All temperatures are stated in degree centigrades.

Examples

Example 1 (**Method A)**

Benzoic acid hydrazide (1 mmol) and 2,5-dihydroxy-benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until N'-(2,5-dihydroxy-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 2 (**Method A)**

2-(1H-indol-3-yl)-acetohydrazide (1 mmol) and 2-hydroxy-benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until N'-(2-hydroxy-benzylidene)-2-(1H-indol-3-yl)-acetohydrazide precipitated, which was filtered off and dried under vacuum.

Example 3 (**Method A)**

1-Naphthoic acid hydrazide (1 mmol) and 2,5-dihydroxy-benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until N'-(2,5-dihydroxy-benzylidene)-naphthalene-1-carbohydrazide precipitated, which was filtered off and dried under vacuum.

Example 4 (**Method A)**

3,4,5-Trimethoxy benzoic acid hydrazide (1 mmol) and 2,3,4-trihydroxy-benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 3,4,5-trimethoxy-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 5 (**Method A)**

2-Amino-5-chloro benzoic acid hydrazide (1 mmol) and 2-hydroxy-benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 2-amino-5-chloro-N'-(2-hydroxy-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 6 (**Method A)**

3-Trifluoromethyl benzoic acid hydrazide (1 mmol) and 2,4-dihydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 3-trifluoromethyl-N'-(2,4-dihydroxy-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 7 (**Method A)**

3-Methoxy benzoic acid hydrazide (1 mmol) and 2-hydroxyacetophenone (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 3-methoxy-N'-[1-(2-hydroxy-phenyl)-ethylidene]-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 8 (**Method A)**

3-Methoxy benzoic acid hydrazide (1 mmol) and 2,5-dihydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 3-methoxy-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 9 (**Method A)**

3,4-Dichloro benzoic acid hydrazide (1 mmol) and 2,3,4-trihydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 3,4-dichloro-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 10 (**Method A)**

4-Chloro benzoic acid hydrazide (1 mmol) and 2,5-dihydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 4-

chloro-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 11 (**Method A)**

4-Hydroxy benzoic acid hydrazide (1 mmol) and 2,5-dihydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 4-hydroxy-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 12 (**Method A)**

3,4-Dichloro benzoic acid hydrazide (1 mmol) and 2,5-dihydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 3,4-dichloro-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 13 (**Method A)**

3-Chloro benzoic acid hydrazide (1 mmol) and 2,5-dihydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 3-chloro -N'-(2,5-dihydroxy-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 14 (**Method A)**

4-Hydroxy-3-methoxy benzoic acid hydrazide (1 mmol) and 5-chloro-2-hydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 4-hydroxy-3-methoxy-N'-(5-chloro-2-hydroxy-benzylidene)-benzo-hydrazide precipitated, which was filtered off and dried under vacuum.

Example 15 (**Method A)**

Benzoic acid hydrazide (1 mmol) and 2,5-dihydroxy acetophenone (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until N'-[1-(2,5-dihydroxy-phenyl)-ethylidene]-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 16 (**Method A)**

4-Hydroxy-3-methoxy benzoic acid hydrazide (1 mmol) and 2,5-dihydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until N'-(2,5-dihydroxy-benzylidene)-4-hydroxy-3-methoxy-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 17 (**Method A)**

Benzoic acid hydrazide (1 mmol) and 2-hydroxy-5-methyl benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until N'-(2-hydroxy-5-methyl-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 18 (**Method A)**

2-Methylamino-benzoic acid hydrazide (1 mmol) and 5-chloro-2-hydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 2-methylamino-N'-(5-chloro-2-hydroxy-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 19 (**Method A)**

2-Methylamino-benzoic acid hydrazide (1 mmol) and 2,5-dihydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 2-methylamino-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 20 (**Method A)**

3-Methyl-benzoic acid hydrazide (1 mmol) and 5-chloro-2-hydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 3-methyl-N'-(5-chloro-2-hydroxy-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 21 (**Method A)**

3-Trifluoromethyl-benzoic acid hydrazide (1 mmol) and 5-chloro-2-hydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was

stirred until 3-trifluoromethyl-N'-(5-chloro-2-hydroxy-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 22 (**Method A)**

2-Methylamino-benzoic acid hydrazide (1 mmol) and 2-hydroxy acetophenone (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 2-methylamino-N'-[1-(2-hydroxy-phenyl)-ethylidene]-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 23 (**Method A)**

Benzoic acid hydrazide (1 mmol) and 2-acetamino acetophenone (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until N-[2-[1-(2-benzoyl-hydrazono)-ethyl]-phenyl]-acetamide precipitated, which was filtered off and dried under vacuum.

Example 24 (**Method B**)

4-Chlorobenzhydrazide (1 mmol) and 2-amino acetophenone (1 mmol) were dissolved in 20 ml of ethanol. The mixture was refluxed for 60 hours and stirring was then continued at ambient temperature. After several days 4-chloro-N'-[1-(2-amino-phenyl)-ethylidene]-benzohydrazide precipitated. The product was filtered and dried under vacuum.

Example 25 (**Method B)**

3-Methoxy benzhydrazide (1 mmol) and 2-amino acetophenone (1 mmol) were dissolved in 20 ml of ethanol. The mixture was refluxed for 60 hours and stirring was then continued at ambient temperature. After several days 3-methoxy-N'-[1-(2-amino-phenyl)-ethylidene]-benzohydrazide precipitated. The product was filtered and dried under vacuum.

Example 26 (**Method A)**

Benzoic acid hydrazide (1 mmol) and 2,3-dihydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until N'-(2,3-dihydroxy-

benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 27 (**Method A)**

3-Methoxy benzoic acid hydrazide (1 mmol) and 2-hydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 3-methoxy-N'-(2-hydroxy-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 28 (**Method A)**

Benzoic acid hydrazide (1 mmol) and 2,3,4-trihydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 29 (**Method A)**

Benzoic acid hydrazide (1 mmol) and 2,3,5-trihydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until N'-(2,3,5-trihydroxy-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 30 (**Method A)**

3,4,5-Trimethoxy benzoic acid hydrazide (1 mmol) and 2,3,5-trihydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 3,4,5-trimethoxy-N'-(2,4,5-trihydroxy-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 31 (**Method A)**

4-Bromo benzoic acid hydrazide (1 mmol) and 2-hydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 4-bromo-N'-(2-hydroxy-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 32 (**Method A**)

3-Trifluoromethyl benzoic acid hydrazide (1 mmol) and 2-hydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 3-trifluoromethyl-N'-(2-hydroxy-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 33 (**Method A**)

3-Methyl benzoic acid hydrazide (1 mmol) and 2,5-dihydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 3-methyl-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 34 (**Method A**)

3-Trifluoromethyl benzoic acid hydrazide (1 mmol) and 2,5-dihydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 3-trifluoromethyl-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 35 (**Method B**)

4-Hydroxy benzhydrazide (1 mmol) and 2,5-dihydroxy acetophenone (1 mmol) were dissolved in 20 ml of ethanol. The mixture was refluxed for 60 hours and stirring was then continued at ambient temperature. After several days 4-hydroxy-N'-[1-(2,5-dihydroxy-phenyl)-ethylidene]-benzohydrazide precipitated. The product was filtered and dried under vacuum.

Example 36 (**Method A**)

4-Chloro benzoic acid hydrazide (1 mmol) and 2-hydroxy-3-chloro benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 4-chloro-N'-(2-hydroxy-3-chloro-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 37 (**Method A**)

4-Chloro benzoic acid hydrazide (1 mmol) and 2,4-dihydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 3-chloro-N'-(2,4-dihydroxy-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 38 (**Method A)**

3-Chloro benzoic acid hydrazide (1 mmol) and 2-hydroxy-5-chloro benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 4-chloro-N'-(2-hydroxy-5-chloro-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 39 (**Method A)**

4-Methoxy benzoic acid hydrazide (1 mmol) and 2,3,4-trihydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 4-methoxy-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 40 (**Method A)**

3,4-Dichloro benzoic acid hydrazide (1 mmol) and 2,3-dihydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 3,4-dichloro-N'-(2,3-dihydroxy-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 41 (**Method A)**

3,5-Bis-(trifluoromethyl)-benzoic acid hydrazide (1 mmol) and 2,3,4-trihydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 3,5-Bis-(trifluoromethyl)-N'-(2,3,4-trihydroxy-benzylidene)-benzo-hydrazide precipitated, which was filtered off and dried under vacuum.

Example 42 (**Method A)**

3-Chloro-2-pyrrol-1-yl benzoic acid hydrazide (1 mmol), of which the synthesis is described in examples 54-56, and 2,3,4-trihydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 3-chloro-2-pyrrol-1-

yl-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 43 (**Method A)**

3-Chloro-2-pyrrol-1-yl benzoic acid hydrazide (1 mmol) , of which the synthesis is described in examples 54-56, and 2-hydroxy-3,5-dichloro benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 3-chloro-2-pyrrol-1-yl-N'-(2-hydroxy-3,5-dichloro-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 44 (**Method A)**

2-Pyrrol-1-yl benzoic acid hydrazide (1 mmol) and 2,3,5-trihydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 2-pyrrol-1-yl-N'-(2,3,5-trihydroxy-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 45 (**Method A)**

4-Chloro-3-trifluoromethyl benzoic acid hydrazide (1 mmol) and 2,3,4-trihydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 4-chloro-3-trifluoromethyl-N'-(2,3,4-dihydroxy-benzylidene)-benzo-hydrazide precipitated, which was filtered off and dried under vacuum.

Example 46 (**Method A)**

4-Chloro-3-trifluoromethyl benzoic acid hydrazide (1 mmol) and 2-hydroxy-3,5-dichloro benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 4-chloro-3-trifluoromethyl-N'-(2-hydroxy-3,5-dichloro-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 47 (**Method A)**

4-Chloro benzoic acid hydrazide (1 mmol) and 2,4,5-trihydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 4-

chloro- -N'-(2,3,4-trihydroxy benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 48 (**Method A)**

Benzoic acid hydrazide (1 mmol) and 2-hydroxy-3,5-dichloro benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until N'-(2-hydroxy-3,5-dichloro-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 49 (**Method A)**

3-Chloro benzoic acid hydrazide (1 mmol) and 2,3,4-trihydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 3-chloro-N'-(2,3,4-trihydroxy benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 50 (**Method A)**

3-Trifluoromethyl benzoic acid hydrazide (1 mmol) and 2,3,5-trihydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 3-trifluoromethyl-N'-(2,3,5-trihydroxybenzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 51 (**Method A)**

3-Trifluoromethyl benzoic acid hydrazide (1 mmol) and 2,3,4-trihydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 3-trifluoromethyl-N'-(2,3,4-trihydroxybenzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 52 (**Method A)**

3,4-Dichloro benzoic acid hydrazide (1 mmol) and 2,3,4-trihydroxy acetophenone (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 3,4-dichloro-N'-[1-(2,3,4-dihydroxy-phenyl)-ethylidene]-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 53 (**Method A)**

3,4-Dichloro benzoic acid N-methyl hydrazide (1 mmol), of which the synthesis is described in example 57, and 2,3,4-trihydroxy benzaldehyde (1 mmol) were suspended in 15 ml of ethanol. The mixture was stirred until 3,4-dichloro-N-methyl-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide precipitated, which was filtered off and dried under vacuum.

Example 54 Synthesis of 3-chloro-2-pyrrol-1-yl-benzoic acid

3-Chloro-2-amino benzoic acid (2 g) and 2,5-dimethyl-tetrahydrofuran (1.6 g) were dissolved in dioxane (10 ml). To this mixture pyridine hydrochloride (700 mg) was added. The mixture was stirred at room temperture under an argon atmosphere for 16 hours followed by 3 hours at 80 °C. The solvents were completely removed in vacuo and the residue was separated between ethyl ether and water. The organic phase was washed with brine, dried with magnesium sulfate. The solvents were completely removed in vacuo. 3-Chloro-2-pyrrol-1-yl-benzoic acid was obtained by crystalization in ethyl acetate / hexane. After the crystals were dissolved in ethyl acetate and this solution was filtered over active carbon, pure 3-chloro-2-pyrrol-1-yl-benzoic acid was obtained by removal of the solvent.

MS: ESI- 220u, 222u

Example 55 Synthesis of 3-chloro-2-pyrrol-1-yl-benzoic acid methyl ester

3-Chloro-2-pyrrol-1-yl-benzoic acid (1.6 g) was dissolved in methanol (30 ml) and concentrated sulfuric acid (0.5 ml) was added. The mixture was kept under reflux for 5.5 hours, cooled to room temperature, cautiously poured on aqueous sodium hydrogencarbonate solution. To this mixture ethyl acetate was added, the layers were separated, the organic layer was washed with brine, dried with magnesium sulfate and the solvents were removed in vacuo. The compound was pure on TLC.

TLC: (plates: Machery Nagel polygram SIL/UV, solvent hexane / ethyl acetate 4/1)

Rf 0.5

IR: film C=O 1728.7/cm

Example 56 Synthesis of 3-chloro-2-pyrrol-1-yl-benzoic acid hydrazide

3-Chloro-2-pyrrol-1-yl-benzoic acid methyl ester (1.45 g) and hydrazine hydrate (80% in water, 750 mg) were dissolved in ethanol (10 ml) and refluxed over night. The solvents were removed to obtain a pure solid.

MS ESI+ 236u, 238 u

Example 57 Synthesis of 3,4-dichloro-benzoic acid N-methyl hydrazide

3,4-Dichloro-benzoyl chloride (4.18 g) was dissolved in methylene chloride (20 ml). To this solution methyl hydrazine (4.0ml) was added. After stirring the solution for 90 minutes the mixture was distributed between methylene chloride and water. The layers were separated, the aqueous layer was extracted several times with methylene chloride, the organic layers were combined, and the solvents were removed in vacuo. After column chromatography pure compound was obtained.

TLC: (plates: Machery Nagel polygram SIL/UV, solvent hexane / ethyl acetate 3/1)

Rf 0.15

The identity and purity of the end products of examples 1-53 was examined by MS-spectroscopy. The applied method was APCI, if not otherwise stated as ESI.

m/e values for the positive and negative ion signals which are set forth in the **table 3** below.

Compounds	Example	Method	molecular weight in g/mol	MS pos mode m/e in u	MS neg mode m/e in u
N'-(2,5-Dihydroxy-benzylidene)-benzohydrazide	1	A	256	257	255
N'-(2-Hydroxy-benzylidene)-2-(1H-indol-3-yl)-acetohydrazide	2	A	293	294	292
N'-(2,5-Dihydroxy-benzylidene)-naphthalene-1-carbohydrazide	3	A	306	307	305

3,4,5-Trimethoxy-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	4	A	362	363	361
2-Amino-5-chloro-N'-(2-hydroxy-benzylidene)-benzohydrazide	5	A	289.7	290	288
3-Trifluoromethyl-N'-(2,4-dihydroxy-benzylidene)-benzohydrazide	6	A	324	325 (ESI)	nd
3-Methoxy-N'-[1-(2-hydroxy-phenyl)-ethylidene]-benzohydrazide	7	B	284	285	283
3-Methoxy-N'-(2,5-dihydroxy-benzylidene)- benzohydrazide	8	A	286	287	285
3,4-Dichloro-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	9	A	341	341, 343, 345 (ESI)	nd
4-Chloro-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide	10	A	290.7	291	289
4-Hydroxy-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide	11	A	272	273	271
3,4-Dichloro-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide	12	A	325	325/327	323/325
3-Chloro-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide	13	A	290	291	289
4-Hydroxy-3-methoxy-N'-(5-chloro-2-hydroxy-benzylidene)-benzohydrazide	14	A	320.7	321	319

N'-[1-(2,5-Dihydroxy-phenyl)-ethylidene]-benzohydrazide	15	A	270	271	269
N'-(2,5-Dihydroxy-benzylidene)-4-hydroxy-3-methoxy-benzohydrazide	16	A	302	303	301
N'-(2-Hydroxy-5-methyl-benzylidene)-benzohydrazide	17	A	254	255	253
2-Methylamino-N'-(5-chloro-2-hydroxy-benzylidene)-benzohydrazide	18	A	303.7	304	302
2-Methylamino-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide	19	A	285	286	284
3-Methyl-N'-(5-chloro-2-hydroxy-benzylidene)-benzohydrazide	20	A	288.7	289	287
3-Trifluoromethyl-N'-(5-chloro-2-hydroxy-benzylidene)-benzohydrazide	21	A	342.7	343	341
2-Methylamino-N'-[1-(2-hydroxy-phenyl)-ethylidene]-benzohydrazide	22	A	283	284	282
N-[2-[1-(2-Benzoyl-hydrazono)-ethyl]-phenyl]-acetamide	23	A	295	296	294
4-Chloro-N'-[1-(2-amino-phenyl)-ethylidene]-benzohydrazide	24	B	287.7	288	286
3-Methoxy-N'-[1-(2-amino-phenyl)-ethylidene]-benzohydrazide	25	B	283	284	282
N'-(2,3-Dihydroxy-benzylidene)-benzohydrazide	26	A	256	nd	255

3-Methoxy-N'-(2-hydroxy-benzylidene)-benzohydrazide	27	A	270	271	269
N'-(2,3,4-Trihydroxy-benzylidene)-benzohydrazide	28	A	272	273	271
N'-(2,4,5-Trihydroxy-benzylidene)-benzohydrazide	29	A	272	273	271
3,4,5-Trimethoxy-N'-(2,4,5-trihydroxy-benzylidene)-benzohydrazide	30	A	362	363	361
4-Bromo-N'-(2-hydroxy-benzylidene)-benzohydrazide	31	A	319	319, 321	317, 319
3-Trifluoromethyl-N'-(2-hydroxy-benzylidene)-benzohydrazide	32	A	308	309	307
3-Methyl-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide	33	A	270	271	269
3-Trifluoromethyl-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide	34	A	324	325	323
4-Hydroxy-N'-[1-(2,5-dihydroxy-phenyl)-ethylidene]-benzohydrazide	35	B	286	nd	285 (ESI)
4-chloro-N'-(2-hydroxy-3-chloro-benzylidene)-benzohydrazide	36	A	274.7	nd	273,275
4-Chloro-N'-(2,4-dihydroxy-benzylidene)-benzohydrazide	37	A	289	nd	289, 291
3-Chloro-N'-(2-hydroxy-5-chloro-benzylidene)-benzohydrazide	38	A	309	nd	307, 309
4-Methoxy-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	39	A	302	303(ESI)	nd

3,4-Dichloro-N'-(2,3-dihydroxy-benzylidene)-benzohydrazide	40	A	325	325, 357 (ESI)	nd
3,5-Bis-(trifluoromethyl)-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	41	A	308	309 (ESI)	nd
3-Chloro-2-pyrrol-1-yl-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	42	A	371.7	nd	370, 372 (ESI)
3-Chloro-2-pyrrol-1-yl-N'-(2-hydroxy-3,5-dichloro-benzylidene)-benzohydrazide	43	A	408.7	nd	406, 408, 410 (ESI)
2-Pyrrol-1-yl-N'-(2,4,5-trihydroxy-benzylidene)-benzohydrazide	44	A	337	nd	336(ESI)
4-Chloro-3-trifluoromethyl-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	45	A	374.7	nd	373, 375 (ESI)
4-Chloro-3-trifluoromethyl-N'-(2-hydroxy-3,5-dichloro-benzylidene)-benzohydrazide	46	A	411.6	nd	409, 411, 413, 414 (ESI)
4-Chloro-N'-(2,4,5-trihydroxy-benzylidene)-benzohydrazide	47	A	306.7	307, 309	305, 307
N'-(2-Hydroxy-3,5-dichloro-benzylidene)-benzohydrazide	48	A	309	309, 311, 313	307, 309, 311
3-Chloro-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	49	A	306.7	307, 309 (ESI)	nd
3-Trifluoromethyl-N'-(2,4,5-trihydroxy-benzylidene)-benzohydrazide	50	A	340	341 (ESI)	nd
3-Trifluoromethyl-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	51	A	340	341 (ESI)	nd

3,4-Dichloro-N'-[1-(2,3,4-dihydroxy-phenyl)-ethylidene]-benzohydrazide	52	A	355	nd	355, 357, 359 (ESI)
3,4-Dichloro-N-methyl-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	53	A	355	nd	353, 355, 357

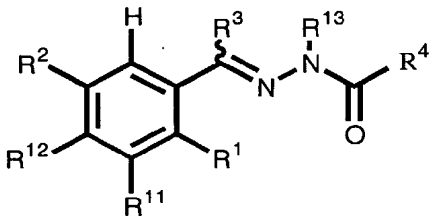
nd means not determined

List of abbreviations

APCI	atmospheric pressure ionization
ESI	electro spray ionization
IR	infrared spectroscopy
MIC	minimal inhibitory concentration
MS	mass spectroscopy
TLC	thin layer chromatography

Claims

1. Compounds of the general formula **1**,



1

wherein R^1 represents lower alkyl-carbonylamino; formylamino; amino; hydroxy;

R^2 represents hydrogen; hydroxy; lower alkyl; fluoro; chloro;

R^3 represents hydrogen; methyl; ethyl; isopropyl;

R^{11} represents hydrogen; hydroxy; lower alkyl; lower alkoxy; fluoro; chloro; amino;

R^{12} represents hydrogen; hydroxy; lower alkyl; lower alkoxy; fluoro; chloro; amino

R^{13} represents hydrogen; lower alkyl

R^4 represents aryl; arylmethyl; indoyl methyl; mono-, di- or tri- substituted aryl, arylmethyl, which substituents may lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy, N-pyrrolyl, 2-pyrrolyl, 3, pyrrolyl and which substituents may be the same or different;

in case R^1 represents amino and R^2, R^{11}, R^{12}, R^{13} and R^3 represent hydrogen, R^4 is not unsubstituted phenyl; phenylmethyl; 2-amino-phenyl; 2-hydroxy-phenyl; 4-chloro-phenyl;

in case R^1 represents amino and R^2, R^{11}, R^{12} and R^{13} represent hydrogen and R^3 represents methyl, R^4 is not unsubstituted phenyl; 2-hydroxy-phenyl;

in case R^1 represents methyl-carbonylamino and R^2, R^3, R^{11}, R^{13} and R^{12} represent hydrogen, R^4 is not 4-hydroxy-3-methoxy-phenyl;

in case R^1 is hydroxy and R^2, R^{11}, R^{12} and R^{13} represent hydrogen and R^3 represents methyl, R^4 is not unsubstituted phenyl; 4-methyl-phenyl; 2-methyl-phenyl; 2-hydroxy-phenyl; 4-methoxy-phenyl; 4-chloro-phenyl; 2-chloro-phenyl; 2,4,6-trimethyl-phenyl;

in case R^1 is hydroxy and R^2, R^{11}, R^{12} and R^{13} represent hydrogen and R^3 represents ethyl, R^4 is not unsubstitued phenyl or 2-hydroxy-phenyl;

in case R^1 is hydroxy and R^2, R^{11}, R^{12} and R^3 represent hydrogen and R^{13} represents methyl, R^4 is not unsubstituted phenyl;

in case R^1 is hydroxy and R^2, R^{11}, R^{12}, R^{13} and R^3 represent hydrogen, R^4 is phenyl substituted with 2-trifluoromethyl, 3-trifluoromethyl, 3-methoxy or (2-amino-5-chloro);

in case R^1 and R^{11} represent hydroxy and R^2, R^3, R^{12} and R^{13} represent hydrogen, R^4 is not 2-chloro-phenyl;

in case R^1 is hydroxy and R^{11} is methoxy and R^2, R^3, R^{12} and R^{13} represent hydrogen, R^4 is not unsubstituted phenyl; 2-hydroxy-phenyl; 2-chloro-phenyl; 4-hydroxy-3-methoxy-phenyl; 5-chloro-2-hydroxy-phenyl; 2-(3-hydroxy)-naphthyl; 2,4-dichloro-phenyl; 4-amino-3,5-dichloro-phenyl; 5-bromo-2-hydroxy-phenyl;

in case R^1, R^{11} and R^{12} represent hydroxy and R^2 and R^{13} represent hydrogen and R^3 is methyl, R^4 is not unsubstituted phenyl;

in case R^1 and R^{12} represent hydroxy and R^2, R^3, R^{11} and R^{13} represent hydrogen, R^4 is not unsubstituted phenyl; 2-hydroxy-phenyl; 4-methoxy-phenyl; 4-hydroxy-3-methoxy-phenyl; 2,4-dichloro-phenyl;

in case R^1 and R^{12} represent hydroxy and R^2, R^{11} and R^{13} represent hydrogen and R^3 is methyl, R^4 is not unsubstituted phenyl; 2-hydroxy-phenyl;

in case R^1 is hydroxy and R^{12} is methoxy and R^2, R^3, R^{11} and R^{13} represent hydrogen, R^4 is not 4-hydroxy-3-methoxy-phenyl;

in case R^1 is hydroxy and R^{12} is methoxy and R^2, R^{11} and R^{13} represent hydrogen and R^3 is methyl, R^4 is not unsubstituted phenyl;

in case R^1 is hydroxy and R^2 is chloro and R^3, R^{11}, R^{12} and R^{13} represent hydrogen, R^4 is not unsubstituted phenyl; 2-methyl-phenyl; 2-hydroxy-phenyl; 4-hydroxy-phenyl; 4-methoxy-phenyl; 4-chloro-phenyl; 5-chloro-2-hydroxy-phenyl; 2-hydroxy naphth-1-yl; 3-hydroxy naphth-2-yl; 2,4-dichloro-phenyl; 3,4-dichloro-phenyl; 3,4,5-trihydroxy-phenyl; 5-bromo-2-hydroxy-phenyl;

in case R^1 is hydroxy and R^2 and R^{11} represent chloro and R^3, R^{12} and R^{13} represent hydrogen, R^4 is not 2-hydroxy-phenyl; 5-chloro-2-hydroxy-phenyl; 3-hydroxy-naphth-2-yl; 2-hydroxy-3,5-dichloro-phenyl; 5-bromo-2-hydroxy-phenyl; 3,5-dibromo-2-hydroxy-phenyl; N-pyrrolyl;

in case R^1 is hydroxy and R^2 and R^3 represent methyl and R^{11}, R^{12} and R^{13} represent hydrogen, R^4 is not unsubstituted phenyl;

in case R^1 is hydroxy and R^2 is methyl and R^3, R^{11}, R^{12} and R^{13} represent hydrogen, R^4 is not 4-chloro-phenyl; 2-naphthyl; 2-bromo-phenyl; 3-bromo-phenyl; 4-bromo-phenyl;

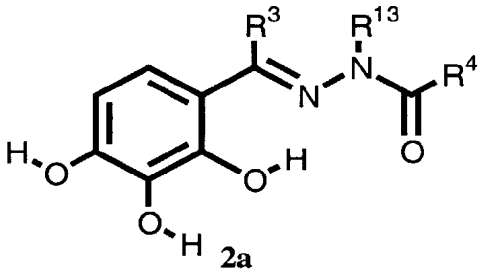
in case R^1 is hydroxy and R^2 is fluoro and R^{11}, R^{12} and R^{13} represent hydrogen and R^3 is methyl or ethyl, R^4 is not 4-fluoro methyl;

in case R^1 and R^{12} represent hydroxy and R^{11} is chloro and R^3 and R^{13} represent hydrogen and R^2 is n-butyl or (3-methyl)-butyl or n-pentyl, R^4 is not 4-amino-2-hydroxy-phenyl;

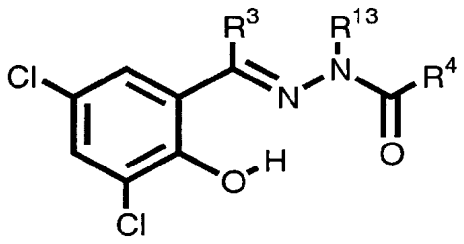
in case R^1 and R^{12} represent hydroxy and R^2 is ethyl or n-butyl or n-hexyl or (3-methyl)-butyl and R^3, R^{11} and R^{13} represent hydrogen, R^4 is not unsubstituted phenyl, 4-amino-phenyl, 4-hydroxy-phenyl, 2-hydroxy-phenyl, 4-amino-2-hydroxy-phenyl,

and pharmaceutically acceptable salts thereof.

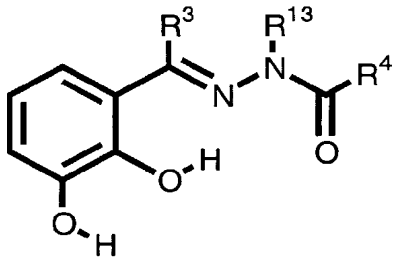
2. Compounds of the formulae **2a-2e**,



2a



2b



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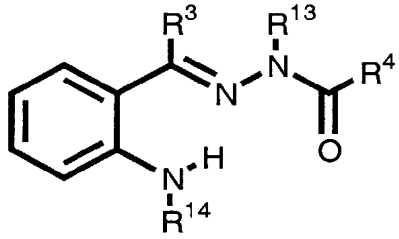
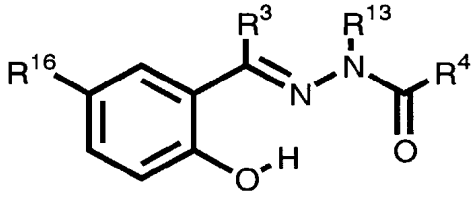


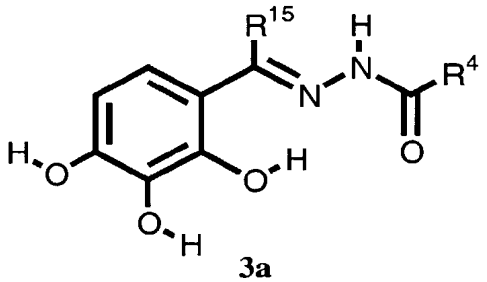
2d



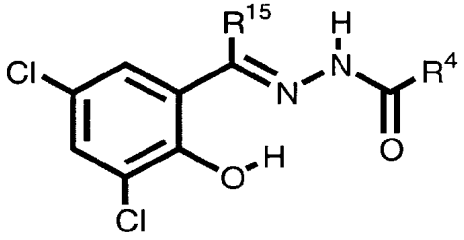
2e

wherein R^3, R^{13} and R^4 have the meaning given in formula **1** and R^{14} is hydrogen, lower alkyl , formyl or acetyl and R^{16} is hydrogen, methyl, fluoro, chloro, hydroxy or ethyl and pharmaceutically acceptable salts thereof.

3. Compounds of the formulae **3a-3e**,



3a



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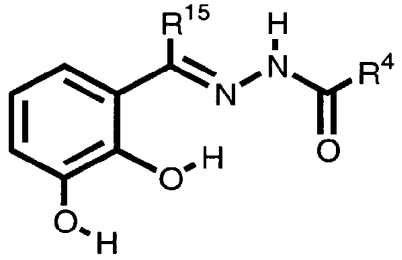

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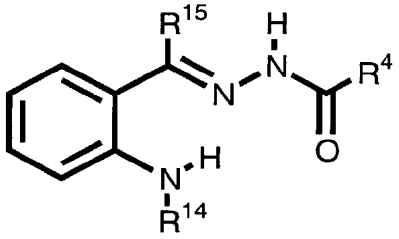
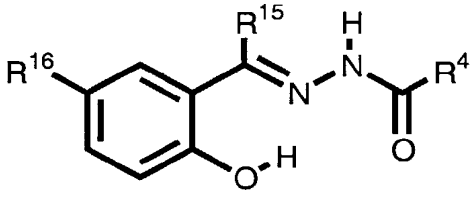


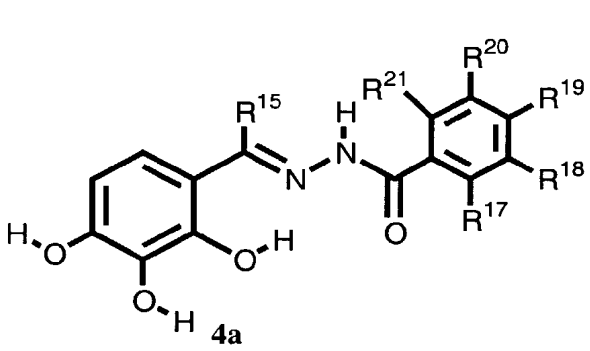
3d



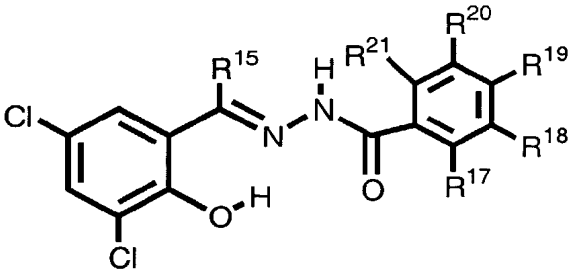
3e

wherein $\mathbf{R^4}$ has the meaning given in formula **1** and $\mathbf{R^{14}}$ is hydrogen, lower alkyl , formyl or acetyl and $\mathbf{R^{16}}$ is hydrogen, methyl, fluoro, chloro, hydroxy or ethyl and $\mathbf{R^{15}}$ is hydrogen, methyl or ethyl and pharmaceutically acceptable salts thereof.

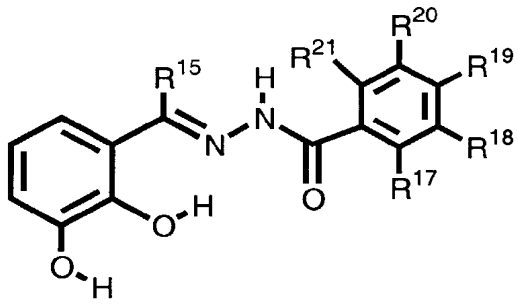
4. Compounds of the formulae **4a-f**



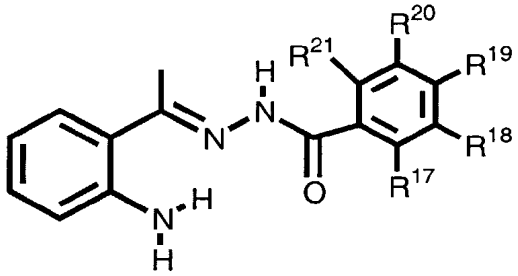
4a



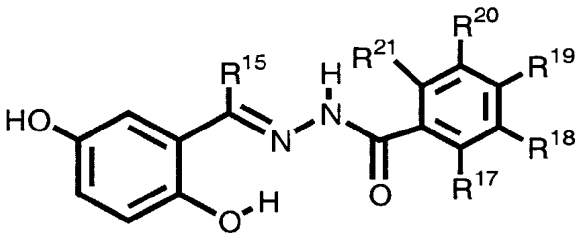
4b



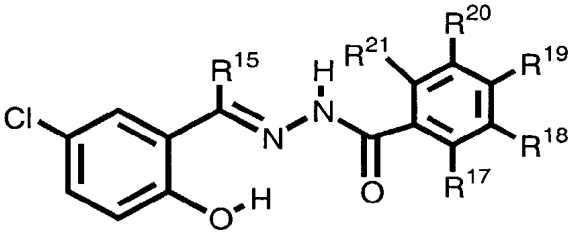
4c



4d



4e



4f

wherein in formula **4a** R^{15} represents hydrogen, methyl or ethyl and, R^{17}, R^{18}, R^{19}, R^{20} and, R^{21}, which may be the same or different, represent hydrogen, N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy, in case R^{15} is methyl either one or two of the substituents R^{17}, R^{18}, R^{19}, R^{20}, R^{21} represent N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy or

wherein in formula **4b** R^{15} represents hydrogen, methyl or ethyl and R^{17}, R^{18}, R^{19}, R^{20} and R^{21}, which may be the same or different, represent hydrogen, N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy, in case R^{17} is N-pyrrolyl either one or two of the substituents R^{18}, R^{19}, R^{20}, R^{21} represent lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy or

wherein in formula **4c** R^{15} represents hydrogen, methyl or ethyl and R^{17}, R^{18}, R^{19}, R^{20} and R^{21}, which may be the same or different, represent hydrogen, N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy, in case R^{15} is hydrogen and R^{17} is chloro either one or two of the substituents R^{18}, R^{19}, R^{20}, R^{21} represents, N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino or lower alkylendioxy or

wherein in formula **4d** R^{17}, R^{18}, R^{19}, R^{20} and R^{21}, which may be the same or different, represent hydrogen, N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy, in case R^{17} is hydrogen or hydroxy, either one or two of the substituents R^{18}, R^{19}, R^{20}, R^{21} represent N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy or

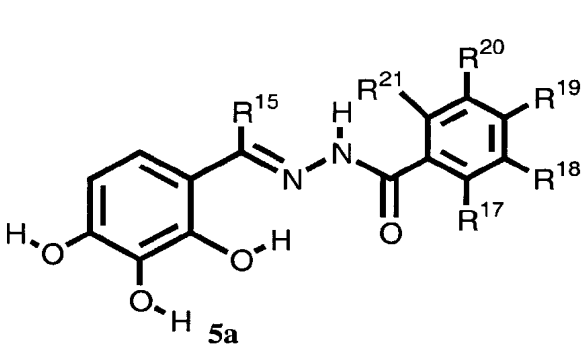
wherein in formula **4e** R^{15} represents hydrogen, methyl, ethyl and R^{17}, R^{18}, R^{19}, R^{20} and R^{21}, which may be the same or different, represent hydrogen, N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy or

wherein in formula **4f** R^{15} represents hydrogen, methyl, ethyl and R^{17}, R^{18}, R^{19}, R^{20} and R^{21}, which may be the same or different, represent hydrogen, N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo,

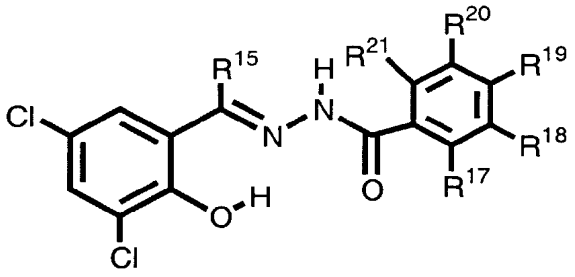
trifluoromethyl, amino, lower alkylamino, lower alkylendioxy, in case R^{15} is hydrogen then at least one of the substituents R^{17}, R^{18}, R^{19}, R^{20} or R^{21} represents pyrrolyl, trifluoromethyl, or lower alkylamino

and pharmaceutically accepable salts thereof.

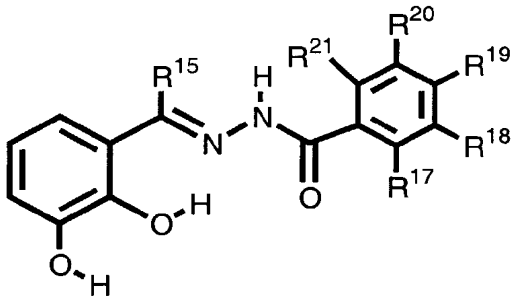
5. Compounds of the formula **5a-e,**



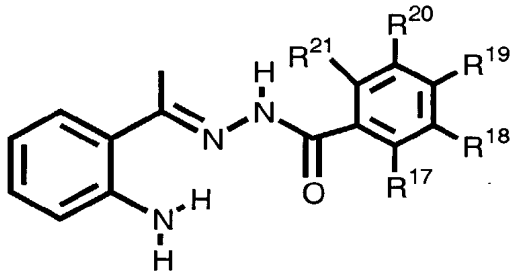
5a



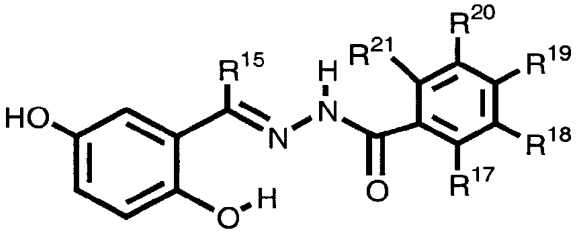
5b



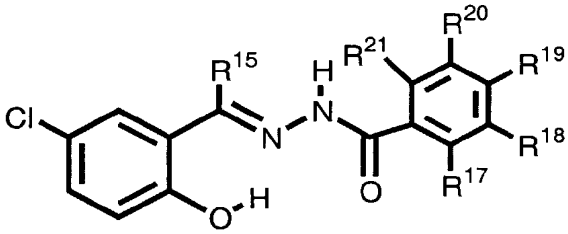
5c



5d



5e



5f

wherein in formula **5a** R^{15} represents hydrogen, methyl or ethyl and R^{17}, R^{18}, R^{19}, R^{20} and R^{21} , which may be the same or different, represent hydrogen, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, lower alkylamino, lower alkylendioxy, with the proviso that one or two of the substituents R^{17}, R^{18}, R^{19}, R^{20} and R^{21} represent trifluoromethyl or chloro or

wherein in formula **5b** R^{15} represents hydrogen, methyl or ethyl and R^{17}, R^{18}, R^{19}, R^{20} and R^{21} , which may be the same or different, represent hydrogen, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, lower alkylamino, lower alkylendioxy, N-pyrrolyl, 2-pyrrolyl or 3-pyrrolyl, with the proviso that one or two of the substituents R^{17}, R^{18}, R^{19}, R^{20} and R^{21} represent N-pyrrolyl, 2-pyrrolyl or 3-pyrrolyl, in case R^{17} represents N-pyrrolyl, at least one of the substituents R^{18}, R^{19}, R^{20} of R^{21} represents lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, lower alkylamino, lower alkylendioxy or

wherein in formula **5c** R^{15} represents hydrogen, methyl or ethyl and R^{17}, R^{18}, R^{19}, R^{20} and R^{21} , which may be the same or different, represent hydrogen, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, lower alkylamino, lower alkylendioxy, with the proviso that one or two of the substituents R^{17}, R^{18}, R^{19}, R^{20} and R^{21} represent chloro or trifluoromethyl or

wherein in formula **5d** R^{17}, R^{18}, R^{19}, R^{20} and R^{21}, which may be the same or different, represent hydrogen, lower alkyl, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy, with the proviso that one or two of the substituents R^{17}, R^{18}, R^{19}, R^{20} and R^{21} represent chloro, methoxy, methyl or trifluoromethyl or

wherein in formula **5e** R^{15} represents hydrogen, methyl, ethyl and R^{17}, R^{18}, R^{19}, R^{20} and R^{21}, which may be the same or different, represent hydrogen, N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy, with the proviso that one or two of the substituents R^{17}, R^{18}, R^{19}, R^{20} and R^{21} represent chloro, methoxy, methyl of trifluoromethyl or

wherein in formula **5f** R^{15} represents hydrogen, methyl, ethyl and R^{17}, R^{18}, R^{19}, R^{20} and R^{21}, which may be the same or different, represent hydrogen, N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy, with the proviso that

in case R^{15} is hydrogen at least one of the substituents R^{17}, R^{18}, R^{19}, R^{20} and R^{21} represents N-pyrroly, 2-pyrrolyl, 3-pyrrolyl, trifluoromethyl or lower alkylamino

and pharmaceutically acceptable salts thereof.

6. The end products as described in Examples 1 to 53 and pharmaceutically acceptable salts thereof.

7. Compounds as claimed in claims 1 to 6

N'-(2,5-Dihydroxy-benzylidene)-benzohydrazide
N'-(2-Hydroxy-benzylidene)-2-(1H-indol-3-yl)-acetohydrazide
N'-(2,5-Dihydroxy-benzylidene)-naphthalene-1-carbohydrazide
3,4,5-Trimethoxy-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide
2-Amino-5-chloro-N'-(2-hydroxy-benzylidene)-benzohydrazide
3-Trifluoromethyl-N'-(2,4-dihydroxy-benzylidene)-benzohydrazide
3-methoxy-N'-[1-(2-hydroxy-phenyl)-ethylidene]- benzohydrazide
3-Methoxy-N'-(2,5-dihydroxy-benzylidene)- benzohydrazide
3,4-Dichloro-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide
4-Chloro-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide
4-Hydroxy-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide
3,4-Dichloro-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide
3-Chloro-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide
4-Hydroxy-3-methoxy-N'-(5-chloro-2-hydroxy-benzylidene)-benzohydrazide
N'-[1-(2,5-Dihydroxy-phenyl)-ethylidene]-benzohydrazide
N'-(2,5-Dihydroxy-benzylidene)-4-hydroxy-3-methoxy-benzohydrazide
N'-(2-Hydroxy-5-methyl-benzylidene)-benzohydrazide
2-Methylamino-N'-(5-chloro-2-hydroxy-benzylidene)-benzohydrazide
2-Methylamino-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide
3-Methyl-N'-(5-chloro-2-hydroxy-benzylidene)-benzohydrazide
3-Trifluoromethyl-N'-(5-chloro-2-hydroxy-benzylidene)-benzohydrazide
2-Methylamino-N'-[1-(2-hydroxy-phenyl)-ethylidene]-benzohydrazide
N-[2-[1-(2-Benzoyl-hydrazono)-ethyl]-phenyl]-acetamide
4-Chloro-N'-[1-(2-amino-phenyl)-ethylidene]-benzohydrazide
3-Methoxy-N'-[1-(2-amino-phenyl)-ethylidene]-benzohydrazide
N'-(2,3-Dihydroxy-benzylidene)-benzohydrazide
3-Methoxy-N'-(2-Hydroxy-benzylidene)-benzohydrazide

N'-(2,3,4-Trihydroxy-benzylidene)-benzohydrazide
N'-(2,4,5-Trihydroxy-benzylidene)-benzohydrazide
3,4,5-Trimethoxy-N'-(2,4,5-trihydroxy-benzylidene)-benzohydrazide
4-Bromo-N'-(2-hydroxy-benzylidene)-benzohydrazide
3-Trifluoromethyl-N'-(2-hydroxy-benzylidene)-benzohydrazide
3-Methyl-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide
3-Trifluoromethyl-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide
4-Hydroxy-N'-[1-(2,5-dihydroxy-phenyl)-ethylidene]-benzohydrazide
4-chloro-N'-(2-hydroxy-3-chloro-benzylidene)-benzohydrazide
4-Chloro-N'-(2,4-dihydroxy-benzylidene)-benzohydrazide
3-chloro-N'-(2-hydroxy-5-chloro-benzylidene)-benzohydrazide
4-Methoxy-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide
3,4-Dichloro-N'-(2,3-dihydroxy-benzylidene)-benzohydrazide
3,5-Bis-(trifluoromethyl)-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide
3-Chloro-2-pyrrol-1-yl-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide
3-Chloro-2-pyrrol-1-yl-N'-(2-hydroxy-3,5-dichloro-benzylidene)-benzohydrazide
2-Pyrrol-1-yl-N'-(2,4,5-trihydroxy-benzylidene)-benzohydrazide
4-Chloro-3-trifluoromethyl-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide
4-Chloro-3-trifluoromethyl-N'-(2-hydroxy-3,5-dichloro-benzylidene)-benzohydrazide
4-Chloro-N'-(2,4,5-trihydroxy-benzylidene)-benzohydrazide
N'-(2-Hydroxy-3,5-dichloro-benzylidene)-benzohydrazide
3-Chloro-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide
3-Trifluoromethyl-N'-(2,4,5-trihydroxy-benzylidene)-benzohydrazide
3-Trifluoromethyl-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide
3,4-Dichloro-N'-[1-(2,3,4-dihydroxy-phenyl)-ethylidene]-benzohydrazide
3,4-Dichloro-N-methyl-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide

8. Pharmaceutical compositions for the treatment of infections, containing a compound of any one of claims 1 to 7 and usual carrier materials and adjuvants.

9. Pharmaceutical compositions for the treatment of infections caused by Gram positive and Gram negative pathogens, containing a compound of any one of claims 1 to 7 and usual carrier materials and adjuvants.

10. The compounds of any one of the claims 1 to 7 for use as medicaments for the treatment of infections.

11. The compounds of any one of the claims 1 to 7 for use as medicaments for the treatment of infections caused by Gram positive and Gram negative pathogens.

12. The use of one or more compounds of any one of claims 1 to 7 as active ingredients for the production of pharmaceutical compositions for the treatment of infections.

13. The use of one or more compounds of any one of claims 1 to 7 as active ingredients for the production of pharmaceutical compositions for the treatement of infections caused by Gram positive and Gram negative pathogens.

14. A process for the manufacture of pharmaceutical compositions for the treatment of infections containing one or more compounds as claimed in any one of claims 1 to 7 as active ingredients which process comprises mixing one or more active ingredient with pharmaceutically acceptable excipients in a manner known per se.

15. A process for the manufacture of pharmaceutical compositions for the treatment of infections caused by Gram positive and Gram negative pathogens containing one or more compounds as claimed in any one of claims 1 to 7 as active ingredients which process comprises mixing one or more active ingredient with pharmaceutically acceptable excipients in a manner known per se.